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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/943,123 | 08/30/2001 | Yie-Hwa Chang | 16153-8007 | 9303 |

21888 7590 02/12/2003

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| EXAMINER |
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 02/12/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/943,123 | CHANG ET AL. | |
| | Examiner | Art Unit | |
| | MINH-TAM DAVIS | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *6-9 and 11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☑ Interview Summary (PTO-413) Paper No(s). *11* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicant's election with traverse of group 6, claims 6-15, SEQ ID NO:9, in Paper No. 10 is acknowledged.

In a telephonic conversation with Kimberly Lu on 01/30/03, Applicant elected the species 1) CMV promoter and 2) inhibition of cell proliferation of the generic dominant negative MetAP2 activity, which includes inhibition of the cleavage of the N-terminal methionine residue from nascent peptides, promotion of cell proliferation, angiogenesis, immune system function, and the inhibition of p53 activity, but not the regulation of protein synthesis, as disclosed in the specification on p.10, second paragraph.

It is noted that SEQ ID NO:9 is a polynucleotide encoding a variant of human MetAP2, wherein His 231 is replaced with Ala (specification, page 5, lines 25-26). Thus the amino acid sequence encoded by SEQ ID NO:9 is SEQ ID NO:6 wherein the designation Xaa at position 231 is Ala, and other amino acids designated as Xaa are the same as the wild type; which is the same as SEQ ID NO:12 (wild type human MetAP2) wherein His231 of SEQ ID NO:12 is replaced with Ala231.

Applicant cancels claim 10 and non elected claims 1-5, 16-30.

Accordingly, claims 6- 9, 11-15, SEQ ID NO:9, species inhibition of cell proliferation, and CMV promoter, are examined in the instant application. Claims 7-8, 12, drawn to a polynucleotide encoding SEQ ID NO:6 is examined only to the extent of a polynucleotide encoding SEQ ID NO:6, wherein the designation Xaa at position 231 of SEQ ID NO:6 is Ala, and wherein other amino acids designated as Xaa in SEQ ID NO:6 are the same as the wild type amino acids of the human MetAP2. In other word, the

examined SEQ ID NO:6 is the same as SEQ ID NO:12 (wild type human MetAP2), wherein His231 of SEQ ID NO:12 is replaced with Ala231.

**OBJECTION**

1. Claims 6-8, 12 are objected to because part of claims 6-8, 12 encompasses polynucleotides encoding variants of MetAP2 that are not elected, e.g. SEQ ID NO: 10, 11, 18, and polynucleotides encoding SEQ II NO:6, wherein amino acids designated as Xaa in positions other than position 231 are any amino acids other than the wild type amino acids.

2. Claims 7 and 8 are objected to because they are drawn to the same composition. Claim 8 is drawn to a peptide that "consists essentially" of SEQ ID NO:6. The language "consists essentially" of claim 8 is interpreted to mean the same as "comprises" of claim 7.

Applicant is advised that should claim 7 be found allowable, claim 8 will be rejected under 35 U.S.C. 101 as being a substantial duplicate thereof, When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. See MPEP 706.03(k).

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION**

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claims 7 and 8 are drawn to a polynucleotide encoding a peptide "comprising" a fragment of SEQ ID NO:6.

It is noted that a polynucleotide encoding a peptide comprising a fragment of SEQ ID NO:6 encompasses a polynucleotide of any structure and any length, provided it encodes peptide comprising a fragment of SEQ ID NO:6, wherein said fragment could be as little as two amino acids and does not necessarily have cell proliferation inhibiting property.

The specification discloses the variant human polypeptide MetAP2 of SEQ ID NO:6 (p.16, first paragraph).

The claims, as written, encompass polynucleotides which vary substantially in length and also in nucleotide composition.

The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be acheived by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural freatures common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d

1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive strutural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural freatures that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed. Thus, only the isolated polynucleotide of SEQ ID NO: 9, encoding SEQ ID NO: 6, but not the full breadth of the claims meet the written description provisions of 35 USC 112, first paragraph.

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE**

withdrawn amended

Claims 6-9, 11-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:9, encoding a protein which inhibits endothelial cell proliferaton *in vitro*, does not reasonably provide enablement for a polynucleotide encoding a variant type 2 methionine amino peptidase which inhibits cell proliferation *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 6-9, 11-15 are drawn to a polynucleotide encoding a variant type 2 methionine amino peptidase, which inhibits cell proliferation and contains a translation domain, wherein said polynucleotide comprises SEQ ID NO:9.

Claims 6-9, 11-15 encompass a polynucleotide encoding a variant type 2 methionine amino peptidase, which inhibits cell proliferation "in vivo", e.g. cancer cell proliferation.

The specification discloses that a vector comprising SEQ ID NO:9 (AdMAP2 (H231A), when transfected into umbilical vascular endothelial cells *in vitro* inhibits cell proliferation (Example 3, page 34).

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between inhibition of proliferation of cells transfected with SEQ ID NO:9 and *in vivo* inhibition of cell proliferation. The *in vitro* transfection data presented is clearly not drawn to subjects with tumor cells, wherein in transfected cells usually the protein is artificially overexpressed, which is not the same conditions as in vivo conditions. Further,

characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993; 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their

counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the transfected cell data presented in the specification, it could not be predicted that, in the *in vivo* environment, the variant type 2 methionine amino peptidase encoded by SEQ ID NO:9 would inhibit cell proliferation, such as cell proliferation of cancer cells.

Further, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that in the *in vivo* environment, the variant type 2 methionine amino peptidase encoded by SEQ ID NO:9 would inhibit cell proliferation, such as cell proliferation of cancer cells. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens

for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that in the *in vivo* environment, the variant type 2 methionine amino peptidase encoded by SEQ ID NO:9 would inhibit cell proliferation, such as cell proliferation of cancer cells. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

**REJECTION UNDER 35 USC 102**

Claims 6-9 are rejected under 35 USC 102 as being anticipated by Griffith, EC et al, 1998, Proc Natl Acad Sci, USA, 95: 15183-15188, as evidenced by Arfin SM et al, 1995, PNAS USA, 92(17): 7714-7718.

Claims 6-9 are drawn to a polynucleotide encoding a polypeptide wherein said a polypeptide (a) is a variant of type 2 methionine aminopeptidase (MetAP2), (b) inhibits cell proliferation, and contains a translation domain. Said polypeptide comprises SEQ ID NO:6 or a fragment thereof. Said polynucleotide comprises SEQ ID NO:9.

It is noted that the only part of SEQ ID NO:6 that is examined is wild type MetAP2, wherein amino acid Xaa at position 231 is Ala231, and wherein any other Xaa at any other amino acid positions are the same as the wild type amino acids. In other words, the part of SEQ ID NO:6 that is examined is the same as SEQ ID NO:12 (wild type MetAP2), wherein His231 is replaced with Ala231 (p.5, second paragraph).

It is further noted that wild type human polynucleotide MetAP2 and the encoded polypeptide MetAP2 are well known in the art (Arfin SM et al, 1995, PNAS USA, 92(17): 7714-7718 and MPSRCH search reports 2003, us-09-943-123-9.rge, pages 2-3, and us-09-943-123-6.rsp, pages 1-2 ).

The specification discloses SEQ ID NO:9 is a human polynucleotide MetAP2 encoding the human polypeptide MetAP2, wherein His231 is replaced with Ala231 (p. 20, first paragraph). The specification further discloses that MetAP2 consists of two domains: 1) a conserved C-terminal catalytic domain and an N-terminal polylysine domain predicted to mediate ribosome oreIF2 association, named the translation domain (p.12, lines 31-33).

Griffith, EC et al teach construction of a polynucleotide variant of human MetAP2, by mutagenesis at His231 of MetAP2, and that mutation of His231 to H231A results in its complete loss of catalytic activity of MetAP2 (p. 15184, second paragraph, paragraph

under Construction of human MetAP2 mutants, p. 1586, second column, last pargraph, bridging page 1587 and figure 5 on page 1586).

The reference does not specifically teach that the variant of MetAP2 inhibits cell proliferation and contains a translation domain. However, the claimed MetAP2 variant appears to be the same as the prior art MetAP2 variant. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

**REJECTION UNDER 35 USC 103**

Claims 11-15 are rejected under 35 USC 103 as being obvious over Griffith, EC et al, 1998, Proc Natl Acad Sci, USA, 95: 15183-15188, in view of US 6,110744.

Claims 11-15 are drawn to a vector containing a polynucleotide encoding a polypeptide wherein said polypeptide (a) is a variant of type 2 methionine aminopeptidase (MetAP2), (b) inhibits cell proliferation, and contains a translation domain. Said polypeptide is SEQ ID NO:6 and said polynucleotide is SEQ ID NO:9, which is operably linked to a promoter which is CMV. The vector is adenovirus vector.

The teaching of Griffith, EC et al has been set forth above.

Griffith, EC et al do not teach a vector containing a polynucleotide encoding a polypeptide wherein said polypeptide (a) is a variant of type 2 methionine aminopeptidase (MetAP2), (b) inhibits cell proliferation, and contains a translation domain. Griffith, EC et al do not teach that said polypeptide is SEQ ID NO:6 and said polynucleotide is SEQ ID NO:9, which is operably linked to a promoter which is CMV. Griffith, EC et al do not teach that the vector is adenovirus vector.

US 6,110744 teaches adenovirus vector comprising a heterologuous gene and a promoter which is CMV.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to clone the polynucleotide sequence taught by Griffth et al in an adenovirus vector having CMV as a promoter, as taught by US 6,110744, because cloning a sequence into a vector is common in the art, and because adenovirus vector comprising a heterologuous gene and a promoter which is CMV is well known in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-

872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

February 3, 2003

ANTHONY C. CAPUTA
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